

# Saliva and Dental Caries

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**Abstract** – Caries is a unique multifactorial infectious disease. Our understanding of etiological factors, the progress of the disease, and the effectiveness of prophylactic procedures have led us to believe that we understand the disease. However, we still have too few answers to many questions: "Why can we not predict who will get the disease?" "Why do we not become immunized?" "How much saliva is enough?" or "Which salivary components are protective?" and "Which salivary components predispose for caries?" It is generally accepted, however, that saliva secretion and salivary components secreted in saliva are important for dental health. The final result, "caries to be or not to be", is a complex phenomenon involving internal defense factors, such as saliva, tooth surface morphology, general health, and nutritional and hormonal status, and a number of external factors—for example, diet, the microbial flora colonizing the teeth, oral hygiene, and fluoride availability. In this article, our aim is to focus on the effects of saliva and salivary constituents on cariogenic bacteria and the subsequent development of dental caries.

**H**uman saliva not only lubricates the oral tissues, making oral functions such as speaking, eating, and swallowing possible, but also protects teeth and oral mucosal surfaces in different ways. The lubricating and antimicrobial functions of saliva are maintained mainly by resting saliva. Stimulation of saliva results in a flushing effect and the clearance of oral debris and noxious agents.

However, the protective functions of saliva are not limited to the above-mentioned functions. Recent studies have revealed a large number of functions, mediated by both the inorganic and organic components of saliva, that should be considered in assessments of the effects of human saliva on dental caries. Some of these studies have introduced a new approach to dental caries from being a bacterially induced multifactorial disease to a disease which may also be influenced by inherited salivary factors. Such genetically regulated salivary components may influence both the colonization and the clearance of micro-organisms from the oral cavity.

## Caries—Who, When, and Where?

The notion that dental caries in animals is an infectious, transmissible disease was first demonstrated by Keyes (1960). Since then, a group of phenotypically similar bacteria, collectively known as mutans streptococci, has been implicated as the principal bacterial component responsible for the initiation and the development of dental caries (Loesche, 1986).

The tooth surface is unique among all body surfaces in two ways. First, it is a non-shedding hard surface, and, second, this surface is introduced into the human mouth during the first years of life. The earliest point at which the cariogenic mutans streptococci may become established is when the first teeth erupt. Solid surfaces are required for both streptococcal colonization and multiplication (Loesche, 1986).

The relationship between the establishment of mutans streptococci and the initiation of dental caries in young children has been extensively studied. Several studies have shown that children who experience colonization by mutans streptococci early in life are at greater risk of developing dental caries than those who are colonized later (Alaluusua and Renkonen, 1983; Caufield *et al.*, 1993). The extent of colonization of mutans streptococci and also, to some degree, subsequent caries activity experience are often correlated with the mother's salivary levels of mutans streptococci (Li and Caufield, 1995). Once mutans streptococci become established, they are considered difficult to eliminate, and the caries process is made possible.

The current concepts of dental caries focus on the fermentation of carbohydrates by cariogenic-bacteria-producing organic acids. Plaque bacteria produce a variety of end-products that may differ depending on the diet. When fermentable carbohydrates are present, the main organic acids produced are lactic, formic, and acetic acids (Geddes, 1975, 1981). These acids coincide with a pH drop in plaque, resulting in demineralization of the tooth (Loesche, 1986; Nyvad and Fejerskov, 1996) and creating an environment which is advantageous for further growth of *Streptococcus mutans* (Bradshaw *et al.*, 1989; Dashper and Reynolds, 2000). In addition to acid production, mutans streptococci express a wide range of virulence factors that are responsible for the cariogenicity of the dental plaque. However, saliva provides the main host defense systems against these virulence factors, and the balance between de- and remineralization is continuously affected by the interaction of bacterial virulence factors and host defense.

The final result, "caries to be or not to be", is a complex phenomenon (Fig. 1) involving internal defense factors, such as saliva, tooth surface morphology, general health, and nutritional and hormonal status, and a number of external factors—for example, diet, the microbial flora colonizing the teeth, oral hygiene, and fluoride availability. In this article, our aim is to focus on the effects of saliva and salivary constituents on cariogenic bacteria and the subsequent development of dental caries.

## Salivary Flow Rate, Buffer Effect, and Dental Caries

Probably the most important caries-preventive functions of saliva are the flushing and neutralizing effects, commonly referred to as "salivary clearance" or "oral clearance capacity" (Lagerlöf and Oliveby, 1994). In general, the higher the flow rate, the faster the clearance (Miura *et al.*, 1991) and the higher the buffer capacity (Birkhed and Heintze, 1989).

Reduced salivary flow rate and the concomitant reduction of oral defense systems may cause severe caries and mucosal inflammations (Daniels *et al.*, 1975; Van der Reijden *et al.*, 1996). Dental caries is probably the most common consequence of hyposalivation (Brown *et al.*, 1978; Scully, 1986). Caries lesions develop rapidly and also on tooth surfaces that are

### Key Words

Saliva, dental caries, buffer effect, adhesion, aggregation, antimicrobial agents.

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usually not susceptible to caries. Subjects with impaired saliva flow rate often show high caries incidence (Papas *et al.*, 1993; Spak *et al.*, 1994) or caries susceptibility (Heintze *et al.*, 1983). It must be emphasized, however, that no linear relationship exists among salivary secretion rate, caries activity, and DMFS/DMFT values (Birkhed and Heintze, 1989; Russell *et al.*, 1990). Only weak or no association between saliva secretion rates and caries incidence has been shown (Mandel, 1987, 1989; Russell *et al.*, 1991). Major and minor salivary gland secretion rates have also been assessed and correlated to the sensation and complaints of dry mouth (xerostomia), objectively reduced saliva secretion (hyposalivation), as well as to various oral health measures, and yet there is an unanswered question: How much saliva is enough? (Fox *et al.*, 1987; Ship *et al.*, 1991).

The buffer capacity of both unstimulated and stimulated saliva involves three major buffer systems: the bicarbonate ( $\text{HCO}_3^-$ ), the phosphate, and the protein buffer systems. These systems have different pH ranges of maximal buffer capacity (Bardow *et al.*, 2000), the bicarbonate and phosphate systems having pK values of 6.1-6.3 and 6.8-7.0, respectively. Since most of the salivary buffering capacity operative during food intake and mastication is due to the bicarbonate system (based on the equilibrium  $\text{HCO}_3^- + \text{H}^+ \rightleftharpoons \text{CO}_2 + \text{H}_2\text{O}$ ), sufficient saliva flow provides the oral cavity with the neutralizing components (Birkhed and Heintze, 1989). The phosphate and protein buffer systems make a minor contribution to the total salivary buffer capacity, relative to the bicarbonate system. The phosphate system is, in principle, analogous to the bicarbonate system but without the important phase-buffering capacity, and it is relatively independent of the salivary secretion rate.

A low flow rate combined with a low or moderate buffer effect clearly indicates poor salivary resistance against microbial attack (Lagerlöf and Oliveby, 1994). An inverse relationship between buffer capacity and caries experience is well-established according to Ericsson (1959), who evaluated 21 reports published up to 1956. On a population level, salivary flow rate and buffer effect show an inverse correlation (Heintze *et al.*, 1983) with caries susceptibility. Among the elderly, an inverse relationship of salivary buffer capacity in stimulated saliva has been established for both enamel (Guivante-Nabet *et al.*, 1998) and root caries (Ravald and Birkhed, 1991; Lundgren *et al.*, 1998). The salivary buffer effect in unstimulated saliva is sparsely documented. However, Larsen and co-workers (1999) have emphasized that the buffering capacity of unstimulated saliva varies so much that single measurements are not reliable for caries prediction.

The buffer effect of saliva is most obviously also affected by hormonal and metabolic changes, as well as by altered general health. It is generally accepted that the buffer effect is greater in men than in women (Heintze *et al.*, 1983). In women, the buffer effect decreases gradually, independent of flow rate, toward late pregnancy and promptly recovers after delivery

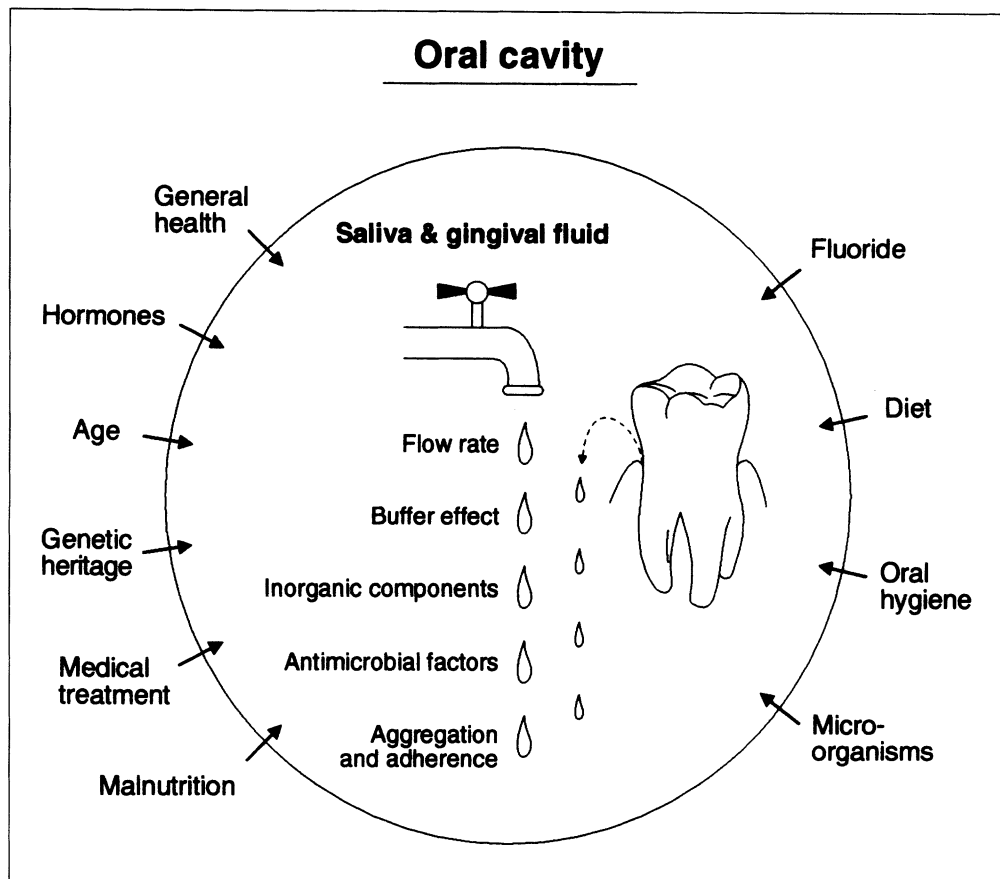


Fig. 1 — A schematic illustration of some of the factors affecting the development of dental caries.

(Laine *et al.*, 1988; Laine and Pienihäkkinen, 2000). The introduction of either hormone replacement therapy in menopausal women (Laine and Leimola-Virtanen, 1996) or low-dose oral contraceptives (Laine *et al.*, 1991) can slightly increase the buffer capacity.

Interestingly, although the secretion rate of stimulated saliva decreases as the degree of malnutrition increases, the buffer effect increases (Johansson *et al.*, 1992). The explanation for this phenomenon is still unclear, but a significant correlation between the degree of malnutrition and the severity of caries has been reported (Johansson *et al.*, 1992).

Carbonic anhydrases (CAs) participate in the maintenance of pH homeostasis in various tissues and biological fluids of the human body by catalyzing the reversible hydration of carbon dioxide,  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}^+$ . Eleven isoenzymes with CA activity have thus far been identified in mammals, and all of them are expressed in the alimentary tract. At least two isoenzymes are involved in salivary physiology (Kadoya *et al.*, 1987). CA II is a cytosolic, high-activity isoenzyme, expressed in the serous acinar cells of the parotid and submandibular glands. It is thought to produce bicarbonate in the saliva. CA VI is the only known secreted CA isoenzyme. It is expressed in the serous acinar cells of the parotid and submandibular glands, where it is secreted into the saliva (Kivelä *et al.*, 1999a).

The physiological role of salivary CA VI has been clarified during recent years (Kivelä *et al.*, 1999a). Low salivary concentrations of CA VI appear to be associated with increased prevalence of caries and acid-peptic diseases (Kivelä *et al.*, 1999a). Kivelä and co-workers (1999b) have shown that salivary CA VI correlates negatively with DMFT- values, especially in individuals with poor oral hygiene. In 1974, Szabó reported higher CA activity levels in caries-free children than in children with active caries. Since there is a positive correlation between CA VI concentration and salivary flow rate, and a negative correlation with the DMFT index, recent

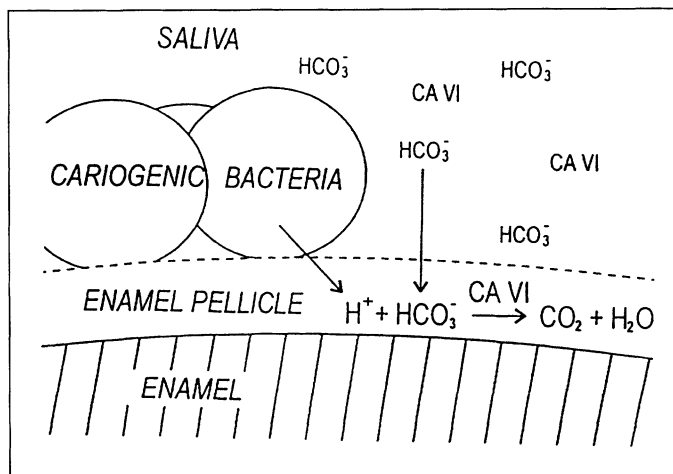


Fig. 2 — Suggested model for the function of CA VI on the dental surface. (Published courtesy of Kivelä *et al.*, 1999a)

research suggests that salivary CA VI plays a role in protecting the teeth from caries (Kivelä *et al.*, 1999a, b).

Contrary to earlier predictions, CA VI does not seem to be directly involved in the regulation of actual salivary pH or buffer capacity, and no correlation has been found between salivary CA VI concentration and mutans streptococci or lactobacilli levels (Kivelä *et al.*, 1999b). CA VI has been reported to bind to the enamel pellicle and retain its enzymatic activity on the tooth surface (Fig. 2; Leinonen *et al.*, 1999). In the enamel pellicle, CA VI may catalyze the conversion of salivary bicarbonate and microbe-delivered hydrogen ions to carbon dioxide and water.

## Homeostasis of Inorganic Components

Human salivary secretions are supersaturated with respect to calcium and phosphate (Hay *et al.*, 1982; Lagerlöf, 1983), but spontaneous precipitation from saliva to dental enamel does not normally occur. This unexpected stability is mediated by a group of salivary proteins, namely, statherin, the acidic PRPs, cystatins, and histatins. These proteins differ from other salivary host defense proteins by having a specific function only for the oral environment, *i.e.*, the maintenance of the homeostasis of the supersaturated state of saliva. Interestingly, these proteins

are multifunctional in that they are partly responsible for the remineralization capacity of saliva, but they also interact with some micro-organisms (Lamkin and Oppenheim, 1993).

Statherin is the only identified inhibitor of primary precipitation in saliva, and a very potent inhibitor of crystal growth. Statherin is a small, 43-amino-acid-containing protein with a highly negatively charged aminoterminal segment (Hay and Moreno, 1989). This negatively charged segment is likely to be the main inhibitory part of the molecule. According to Hay and Moreno (1989), statherin is present in stimulated saliva in concentrations sufficient to inhibit the precipitation of calcium and phosphate salts effectively. More recent studies have shown that statherin may contribute to the early colonization of the tooth surfaces by certain bacteria, such as *Actinomyces viscosus* (Gibbons and Hay, 1988).

The acidic proline-rich proteins (PRPs) account for 25–30% of all proteins in saliva, and they have high affinity for hydroxyapatite *in vitro* (Hay and Moreno, 1989). The acidic PRPs bind free calcium, adsorb to hydroxyapatite surfaces, inhibit enamel crystal growth, and regulate hydroxyapatite crystal structure (Hay and Moreno, 1989). The multifunctional properties of acidic PRPs, like statherins, are shown by their ability to promote the attachment of bacteria to apatitic surfaces (Gibbons and Hay, 1988, 1989; Gibbons *et al.*, 1991). Interestingly, the amount and quality of acidic PRPs, and agglutinins, are found to be different in caries-free and caries-active individuals (Rosan *et al.*, 1982; Stenudd, 1999).

Cystatins form a family of cysteine-containing phosphoproteins, which may play a minor role in the regulation of calcium homeostasis in saliva (Johnsson *et al.*, 1991; Lamkin and Oppenheim, 1993). Phosphorylated and non-phosphorylated cystatins bind to hydroxyapatite, but the role of cystatins in the caries process is unclear.

There are very few reports on the possible correlation between the above-described proteins and dental caries. The fact that, for example, statherin, acidic PRPs, and cysteins play a key role in a protective and reparative system which is important for the integrity of the teeth is obvious. However, there are only two reports on the correlation between cystatin and caries prevalence (Table). Tabak and co-workers (1994) suggest that there is an inverse relationship between the levels of cystatin in resting whole saliva of children and their past and active caries experience, while the other study (Shomers *et al.*, 1982) found no association between cystatin concentration and caries.

TABLE — Numbers of Studies<sup>a</sup> on the Associations Between Salivary Components and Caries

Saliva Component	Pos. Corr. <sup>b</sup>	Neg. Corr.	NS
Cystatins	-	1	1
Statherin	-	-	-
Proline-rich proteins	-	-	1
α-Amylase	-	-	1
Lysozyme	-	1	10
Lactoferrin	-	-	7
Peroxidases	2	-	9
HOSC/OSCN <sup>c</sup>	1	2	4
Histatins	-	1	-
slgA			
DMFT/DMFS	1	7	6
Active caries lesions	1	5	3
Mutans streptococci	1	5	3
IgG <sup>c</sup>	2	1	5

<sup>a</sup> List of references can be requested from the authors.

<sup>b</sup> The outcomes of the studies are marked as follows: pos. corr. = positive correlation; neg. corr. = negative correlation; NS = no significant association.

<sup>c</sup> Only studies with salivary IgG are included.

## Salivary Adhesion and Bacteria-aggregating Proteins in Dental Caries

The acquired enamel pellicle is a thin film consisting mainly of salivary proteins selectively absorbed to the surface of the enamel. The pellicle protects the enamel from dissolution. Diffusion fluxes are reduced by 50% in the presence of pellicle (Zahradnik *et al.*, 1976), leading to a decreased demineralization potential of the acids secreted by bacteria (Zahradnik *et al.*, 1977). The pellicle is also a base to which the bacteria can adhere when they enter the oral cavity. The binding of bacteria is mediated by non-specific electrostatic and van der Waals forces, but also by specific interactions between bacteria and the proteins on the salivary pellicle. Thus, colonization of microbial flora on the tooth surface is strongly modified by salivary proteins (Gibbons, 1989). Several proteins-like parotid saliva agglutinins, α-amylase, statherins, mucins, acidic PRPs, and salivary immunoglobulins are reported to bind with oral streptococci (Scannapieco, 1994). These proteins are also found in the salivary pellicle, and therefore, they are likely to mediate the specific adhesion of bacteria to tooth



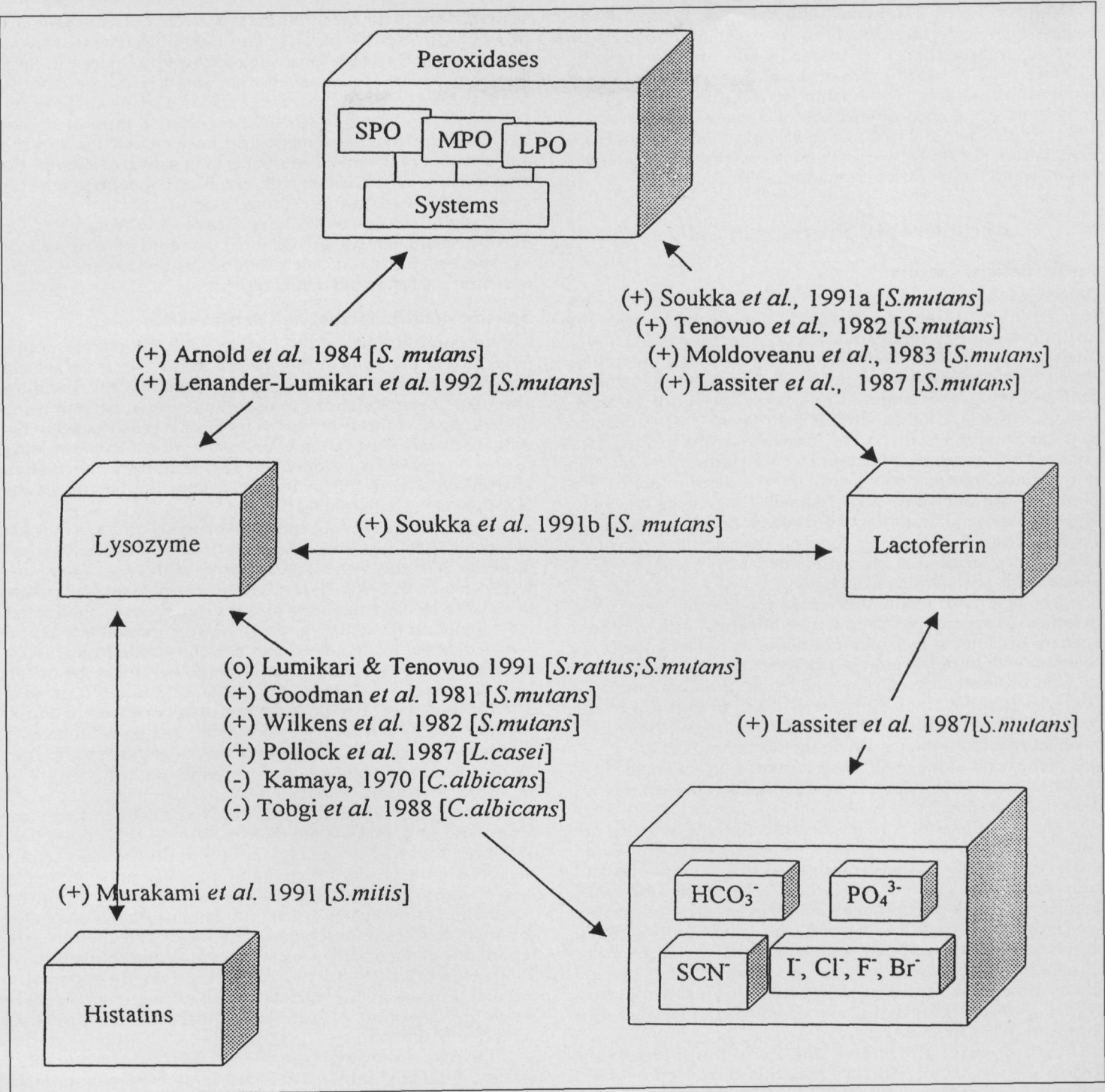


Fig. 3 — Interactions between innate host factors *in vitro*. The target organism studied is indicated in parenthesis. (+) = synergism or additive effect. (-) = inhibitory effect. (0) = no effect. (Published courtesy of Kivelä *et al.*, 1999a)

surfaces. It has been suggested that high-molecular-weight parotid saliva agglutinins, and similar proteins found in submandibular-sublingual saliva, are the most important salivary proteins in promoting the adhesion of *Streptococcus mutans* (Ericson and Rundegren, 1983; Kishimoto *et al.*, 1989; Carlén and Olsson, 1995).

On the other hand, when these same proteins exist in the liquid phase, they may promote bacterial aggregation and, hence, the clearance of bacteria from the oral cavity. The two most abundant agglutinins in saliva are high-molecular-weight agglutinin from parotid saliva and mucins. Of the mucins, the low-molecular-weight form, MG2, is more efficient in bacterial aggregation and clearance than the high-molecular-weight form, MG1

(Tabak, 1995). MG1 and MG2 proteins are products of different genes (Tabak, 1990, 1995), although it has recently been suggested that part of the low-molecular-weight mucins may be derived from high-molecular-weight mucins by the action of proteases in saliva (Slomiany *et al.*, 1996). This study, however, has not been further verified.

The ability of different salivas to promote aggregation or adhesion varies greatly among individuals. It has been speculated that the high aggregation and low adhesion activity of saliva against mutans streptococci could explain the differences in colonization susceptibility among individuals. Indeed, MG1 predominates in the saliva of caries-susceptible subjects, while the level of MG2 appears to be consistently higher in the saliva of caries-resistant

individuals. There is only one study suggesting that mucin protease activity in the saliva of caries-resistant individuals is 3.8-fold greater than that in caries-susceptible subjects (Slomiany *et al.*, 1996). Several studies, however, have reported an inverse relationship between the aggregating activity of saliva and colonization of *S. mutans* (Rosan *et al.*, 1982; Emilson *et al.*, 1989; Carlén *et al.*, 1996), and also a positive correlation between the adhesion-promoting activity of saliva and dental caries (Stenudd, 1999).

## Antimicrobial Proteins in Saliva

### Innate defense factors

The innate defense factors identified in saliva have been extensively studied *in vitro*, and they express different antimicrobial properties (Tenovuo and Lumikari, 1991; Tenovuo *et al.*, 1991). The modes of action of these molecules differ vastly, suggesting a long evolution during which the oral cavity has been exposed to a large variety of bacteria, fungi, viruses, and other noxious substances, *e.g.*, mutagenic and carcinogenic substances, as well as H<sub>2</sub>O<sub>2</sub>. The data obtained so far are mainly from *in vitro* studies, and there is only limited information on how these molecules act *in vivo* (Tenovuo and Lumikari, 1991; Tenovuo *et al.*, 1991). It is well-known that many antimicrobial proteins in saliva interact *in vitro* with each other (Fig. 2). The interactions result in additive, synergistic, or inhibitory effects on mutans streptococci, lactobacilli, or fungi.

The main oral innate defense factors are the peroxidase systems, lysozyme, lactoferrin, and histatins. *In vitro*, these proteins are known to (1) limit bacterial or fungal growth, (2) interfere with bacterial glucose uptake or glucose metabolism, and (3) promote aggregation and, thus, the elimination of bacteria. It should be emphasized that, in addition to the antimicrobial action of both salivary peroxidase and myeloperoxidase systems (Månsson-Rahemtulla *et al.*, 1987), one of the main purposes of these systems is to eliminate H<sub>2</sub>O<sub>2</sub>, which is highly toxic for mammalian cells (Hänström *et al.*, 1983; Tenovuo and Larjava, 1984).

Many of the antimicrobial defense systems in saliva are common to all exocrine secretions such as tears, milk, and seminal, vaginal, and gastrointestinal fluids (Tenovuo and Lumikari, 1991; Tenovuo *et al.*, 1991). Especially lysozyme, lactoferrin, and peroxidases are present in measurable concentrations in all these secretions. These antimicrobial agents are mainly synthesized in, and secreted via, the major or minor salivary glands, but a smaller amount enters the oral cavity from tissue fluid or polymorphonuclear leukocytes (PMNs) *via* the gingival crevicular fluid (Tenovuo and Lumikari, 1991; Tenovuo *et al.*, 1991).

During early childhood, the non-immune salivary factors—*e.g.*, lysozyme, salivary peroxidase, and peroxidase-generated hypothiocyanite (HOSCN/OSCN<sup>-</sup>)—are present at levels similar to those in adults. However, lactoferrin, myeloperoxidase, and total protein are still significantly less abundant (Mandel *et al.*, 1983; Tenovuo *et al.*, 1987). All non-immune defense factors reach adult levels by the early teenage years (Kirstilä *et al.*, 1998) and remain at high concentrations even among elderly people with full dentition. If a considerable number of teeth are extracted, the components derived *via* gingival crevices are diminished (Närhi *et al.*, 1994).

Several attempts have been made to correlate salivary peroxidase activity, peroxidase-produced hypothiocyanite concentrations, lysozyme activity, lactoferrin or apo-lactoferrin concentrations, cystatin, histatin or proline-rich protein concentrations, and amylase activities to general, dental, gingival, or mucosal health (Table). The studies have been both cross-sectional and longitudinal. However, the literature presents controversial results. This may depend on inconsistency in study design, saliva collection methods,

salivary analysis methods, statistical analysis, and the presentation of the results. The available literature was extensively and comprehensively reviewed by Rudney in 1995. Because several studies show that salivary innate defense factors affect cariogenic bacteria such as mutans streptococci, lactobacilli, and fungi *in vitro*, the expectation in most studies has been an inverse relationship between caries and the amounts of antimicrobial components in saliva. However, the only positive relationships with caries might be predicted for proteins that promote adhesion or maintain inorganic component homeostasis in the oral cavity (Rudney, 1995). On the other hand, it must be concluded that it may not be realistic to expect highly significant relationships between any single non-immune factor and dental caries.

### Specific defense factors and dental caries

The immunoglobulins, IgG, IgM, IgA, and secretory IgA (sIgA), form the basis of the specific salivary defense against oral microbial flora, including mutans streptococci. The most abundant Ig in saliva, as in all other human secretions, is dimeric sIgA, which is produced by plasma cells located in the salivary glands. Two IgA subclasses are present in saliva; IgA1 forms the major component of Igs, although the relative amount of IgA2 is higher in saliva than in other secretions (Tappuni and Challacombe, 1994).

In human beings, IgG, mainly of maternal origin, is the only detectable Ig in the saliva of neonates. Salivary IgA is absent at birth but is readily detectable in infants at the age of only one week (Cole *et al.*, 1998). The IgG concentration decreases to non-detectable levels after some months but appears again after tooth eruption (Brandtzaeg, 1989). Low concentrations of IgG can be detected in stimulated parotid saliva (Brandtzaeg, 1989), but most of the IgG detected in whole saliva enters the mouth from the gingival crevicular fluid, thus originating from sera. The formation of specific IgAs in saliva correlates with the colonization of bacteria in the oral cavity. In most children over three years of age, salivary IgAs against mutans streptococci can be detected, and their amount increases with the length of exposure (Smith and Taubman, 1992).

Salivary Igs can bind to the salivary pellicle, and they are found also in dental plaque (Newman *et al.*, 1979; Fine *et al.*, 1984). In the oral cavity, Igs act by neutralizing various microbial virulence factors, limiting microbial adherence, and agglutinating the bacteria, as well as by preventing the penetration of foreign antigens into the mucosa. IgGs are also capable of opsonizing bacteria for phagocytes, which are reported to remain active in dental plaque and saliva (Scully, 1980; Newman, 1990). Phagocytosis may be especially important in modifying microbial flora during tooth eruption when high amounts of IgGs and neutrophils exist in close contact with the teeth.

The role of salivary Igs in dental caries formation is still a matter of debate (Table). There are some experimental data suggesting a protective role of the anti-streptococcal IgGs, mainly measured from serum, against caries and colonization of *S. mutans* in early childhood (Lehner *et al.*, 1978; Aaltonen *et al.*, 1987; Tenovuo *et al.*, 1987) and in adults (Challacombe *et al.*, 1984; Gregory *et al.*, 1990), but also contradictory results exist (Lehtonen *et al.*, 1984; Gråhn *et al.*, 1988; Camling *et al.*, 1991). Conflicting results are also reported for salivary IgA and dental caries, as extensively reviewed recently by Marcotte and Lavoie (1998). Comparison of different studies is complicated, however, since different samples are collected, and in some studies the Ig levels are correlated with DMFT/DMFS scores (that is, past experience of caries), whereas in other studies they are correlated with the presence of active caries (a situation which may take several months to develop), or with the levels of mutans streptococci in the mouth. It must also be noted that the presence of active caries lesions may induce the formation of specific IgGs (Challacombe, 1980; Kirstilä *et al.*, 1998), and that they may remain at a higher level for several weeks or months

after eradication of the lesions. Further, it has been postulated that part of the detected IgAs against mutans streptococci is generated by cross-reactivity with antigens from other bacteria.

Certain diseases, such as selective IgA immunodeficiency, should provide a unique model for the evaluation of the role of sIgA in the colonization of mutans streptococci and, more generally, in oral health. However, even these results are contradictory, and an increased, decreased, or lack of correlation between IgA deficiency and caries susceptibility has been reported (Tenovuo, 1998). Some studies, however, show increasing levels of other antimicrobial factors in the saliva of these patients (Tenovuo, 1998), thus supporting the previous conclusion about the clinical significance of the entire repertoire of antimicrobial components for oral health.

## Concluding Remarks

The infectious nature of dental caries has already been known for decades. Ever since the recognition of *Streptococcus mutans* as the main microbial factor in the etiology of caries disease, a vast amount of work and effort has been devoted to the characterization of this bacterium. The number of published papers on mutans streptococci is enormous, exceeded only by the quantity of publications on *Escherichia coli*.

Today, we already have increased knowledge of the initiation, progression, and transmission of the disease. Still, we cannot fully explain what causes the disease in some persons but not in others, even though cariogenic microbes and other etiological factors are present. Also, the immunization methods against these bacteria are still lacking, even though promising results had already been obtained in animal studies in the 1960s.

The complexity of the oral biofilm and the microbial flora, the metabolic and adherence interactions between bacteria, etc., obviously influence the outcome of the disease. However, phenotypic and genotypic differences inside a bacterial strain should also be recognized. Further, the skewed caries distribution observed nowadays in Western countries suggests that there might also be an important host-derived genetic background for the disease and, thus, the susceptibility for dental caries.

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